REMARKS

The Examiner has restricted claims 1-12 and 23-31 (claims 1 and 23 are independent) to 150 Groups. Specifically, the Examiner has restricted claims 1-7, 11 and 12 to Group 1-10, which are drawn to compositions comprising a plurality of distinct conjugates, each of which comprises a head group and a tail group, based on the chemical or functional characteristics of the head group. The Examiner has also restricted claims 1-12 to Group 11-50, which are drawn to compositions comprising a plurality of distinct conjugates, each of which comprises a head group, a tail group and a spacer group, based on the chemical or functional characteristics of each of the head and spacer groups.

Further, the Examiner has restricted claims 23-30 to Group 51-60, which are drawn to methods for producing compositions comprising a plurality of distinct conjugates, each of which comprises a head group and a tail group, based on the chemical or functional characteristics of the head group. The Examiner has also restricted claims 23-30 to Group 60-100, which are drawn to methods for producing compositions comprising a plurality of distinct conjugates, each of which comprises a head group, a tail group and a spacer group, based on the chemical or functional characteristics of each of the head and spacer groups.

The Examiner has also restricted claim 31 to Group 101-110, which are drawn to methods for producing a molecule for interaction with a ligand, comprising producing compositions comprising a plurality of distinct conjugates, each of which comprises a head group and a tail group, based on the chemical or functional characteristics of the head group. The Examiner has also restricted claim 31 to Group 111-150, which are drawn to methods for producing a molecule for interaction with a ligand, comprising producing compositions comprising a plurality of distinct conjugates, each of which comprises a head group, a tail group and a spacer group, based on the chemical or functional characteristics of each of the head and spacer groups.

In addition, the Examiner has objected to claims 13-22 because those claims do not set forth any steps involved in the method/process. The Examiner, however, has expressed that those claims will be considered for restriction or election of species if the objection is withdrawn. In response to the Examiner's objection to the form of claims 13-22, applicants amended those claims to recite a step.

> The Examiner's reasoning for the Restriction Requirement is as follows. [T]he inventions listed as Groups 1-150 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the technical feature of a composition for interacting with a ligand, which composition comprises a non- covalent association of a plurality of distinct conjugates, each conjugate comprising a head group and a tail group, wherein the tail groups of the conjugates form a hydrophobic aggregation and the conjugates are movable within the association, is taught by Yager et al, US 5,851,536. Yager et al. ... teach compositions comprising "therapeutics" (Th) that are head groups that can be a peptide or polypeptide, high axial ratio forming molecules (HARFM) that are lipid tail groups and spacers. Th can be covalently bound to HARFM. The HARFMs can form aggregates in water because of their hydrophobic tails and can form liposomes, micelles, and lamellar associations. See Figure 5. The compositions of Yager et al. are the same as the compositions of the claimed invention. Therefore, absent evidence to the contrary, the conjugates of Yager are movable in their association and in the presence of a ligand, at least two of the head groups would be appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually.

The Restriction Requirement mailed on September 22, 2004, Page 19.

Applicants traverse. The Examiner assumed that Yager et al. taught "movable" conjugates in their association absent evidence to the contrary. Applicants read Yager as teaching the following:

> Diacetylenic lipid tubules are straight, rigid ...

column 2 line 50 (underline added);

> HARFMs, particularly tubules and cochleate structures, generally are crystalline materials and tend to dissolve only from the surfaces and ends thereof, or perhaps from regions of imperfection in the HAR microstructure.

column 20 lines 7-10 (underline added);

> The tubule morphology is composed of helically-wrapped lipid bilayers that close to form straight, hollow, rigid tubes. Tubules can appear, however, in the presence of minority structures such as open helical ribbons. If given time to anneal, the lipids form closed and uniform tubules. Presumably, the tight crystalline packing of the tubule wall will hinder release of monomeric lipid from the microstructure and insertion of detergent into the tubule except at regions of defects in the crystalline packing such as must occur at tubule ends or at "helical" defects.

column 22 lines 36-38 (underline added); and

> The tight packing of the lipid molecules in the HAR microstructure could afford protection of certain drugs such as peptides from the premature enzymatic hydrolysis ...

column 24 lines 33-36 (underline added). These teachings (rigid tube structures, tight crystalline packing of the tubule wall, crystalline packing, and the tight packing of the lipid molecules in the HAR microstructure) counsel against inferring that the conjugates of Yager are movable in their association, i.e., the mobility of the lipid molecules in Yager's microstructures. On the other hand, applicants could not find any teachings to support the Examiner's assumption of mobility of HARFMs in the microstructure taught in Yager. Therefore, applicants submit that the Examiner's assumption of mobility of the HARFMs taught in Yager cannot stand in light of Yager's contrary teachings.

Further, applicants also submit that the Examiner's another assumption that "in the presence of a ligand, at least two of the head groups would be appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually" also cannot stand without the support of the above-mentioned mobility assumption.

The Examiner's assumption that the head groups taught in Yager form an epitope capable of interacting with the ligand more strongly than each of the head groups individually cannot be favored for additional reasons. Applicants submit that a fair reading of Yager, especially the section describing therapeutics (column 14 line 27 - column 15 line 13), is that an individual therapeutic molecule contemplated by Yager binds its counterpart (whether it be a receptor, a ligand, an antigen, or an antibody) on its own, without help from any neighboring therapeutic molecules. The examples of therapeutics molecules in the above-mentioned section are already independent therapeutic molecules on their own, which means that they already have a complete set of epitopes needed to bind their counterparts to exert their usual therapeutic activities. Therefore, it is hard to imagine that those individual therapeutic molecules cooperatively interact with each other to form one epitope for a stronger binding to a counterpart molecule.

Applicants further submit that the working mechanism of Yager's microstructures counsels against inferring interaction of individual therapeutics molecules with one another in binding their counterparts. The working mechanism is explained in Yager as follows.

> Another object of this invention is to form compounds and compositions comprising drugs or prodrugs associated with HARFMs that continuously release drugs either through dissolution of the molecules from the ends of the microstructures or through enzymatic cleavage.

> Still another object of the present invention concerns using a homogeneous population of HARFMs to dissolve (or be enzymatically degraded) in such a manner that the rate of release of the constituent molecules (or parts thereof) is constant until the microstructures are consumed.

column 5 lines 22-31 (underline added). See also column 7 lines 3-9; column 19 lines 43 - column 20 line 13. The therapeutic molecules (considered a head group by the Examiner) of Yager are released from HARFMs to exert their pharmaceutical activities, and while they are still linked or associated with the microstructure (e.g. HARFMs), they are tightly packed and stored for release. It is hard to imagine that the tightly packed molecules can assume several conformational changes to form one epitope, or that the once released therapeutic molecules come into a close proximity with each other to form an epitope.

Thus, applicants submit that Yager does not render any of the independent claims 1 and 21 (which are linking claims) unpatentable, and respectfully request the Examiner to withdraw the restriction of claims 1-12 to Groups 1-50, claims 23-30 to Groups 51-100 and claims 31 to Groups 101-150 (which applicants believe are restrictions based on the chemical or functional characteristics of the allegedly head and spacer groups taught in Yager).

Restriction of claims 1-12 to Groups 1-50, claims 23-30 to Groups 51-100 and claims 31 to Groups 101-150 has another problem. The instant application teaches:

> Each conjugate in the assembly may have a head group selected from one chemical or biological class or a number of different classes, such as an amino acid or peptide; a peptide analogue; a mono-, di-or poly-saccharide; a mono-, di-or poly-nucleotide; a sterol; an alkaloid; an isoprenoid; an inositol derivative; a single or fused aromatic nucleus; a water-soluble vitamin; a porphyrin or haem nucleus; a phthalocyanine; a metal ion chelate; a water-soluble drug; a hormone; or an enzyme substrate. (Underline added).

Paragraph bridging pages 3 and 4 of the instant application. This paragraph clearly shows that the invention contemplated by the applicants includes a possibility of employing head groups of different classes in one embodiment, e.g., peptide and nucleotide head groups can be employed in one embodiment. Further, the application teaches that the conjugate molecules can have optional spacer groups of varying classes as follows.

> For example, each conjugate may further comprise a spacer group linking the head group to the tail group so as to facilitate presentation of the head group on the surface of the non-covalent association. Such spacer groups are well known and include, for example, amino acids, hydroxy acids, sugars and polyethylene glycol.

The first full paragraph at page 5 of the instant application. The outstanding Restriction Requirement, however, makes it impossible to claim such mixed-class embodiments, and unduly limits applicants' right to seek an appropriate scope of protection to which applicants are entitled.

> The Examiner's reasoning for the Restriction Requirement is as follows. The head and spacers groups of the claimed inventions comprise molecules that do not share a common core structure and do not share common properties. Therefore these claimed inventions further lack unity of invention.

The Restriction Requirement mailed on September 22, 2004, Page 19. Applicants traverse. The head groups can interact with another head group or other head groups to form an epitope. See second full paragraph at Page 2 and Figure 2 of the instant application. The head groups, which are typically non-identical, interact cooperatively to induce biological consequences which the head groups on their own are not capable of eliciting. See Page 3 of the instant application. The spacer groups link the head group to the tail group so as to facilitate presentation of the head group on the surface of the non-covalent association. See Page 5 of the instant application. The functional

nature of these common properties is a natural result of the combinatorial characteristics of the instant invention. See Paragraph bridging page 8 and 9 of the instant application.

These common properties are the special technical features required for unity of invention under PCT Rule 13, which does not exclude functional properties from special technical features. These special technical features are incorporated in all of the pending claims by the claim language: "in the presence of a ligand, at least two of the head groups are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually", and preclude not only the restriction of claims 1-12 to Groups 1-50, claims 23-30 to Groups 51-100 and claims 31 to Groups 101-150, but also the restriction of claims 1-31 into any separate groups because:

> [t]he method for determining unity of invention under PCT Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application: (A) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product; or ..."

MPEP §1850 (8th Edition). Claims 1-12 are directed to a product. Claims 13-22 are directed to the use of the product. Claims 23-31 are specially adapted for the manufacture of the product. Further, if one skilled in the art were to be in possession of claims 23-30, one would be able to come up with currently pending claims 1-22 and 31 without much difficulty.

Therefore, applicants submit that all of the outstanding Restriction Requirement is improper, and respectfully request the Examiner withdraw the entire Restriction Requirement and examine all pending claims although applicants provisionally elect Group 1.

Alternatively, if the Examiner maintains the outstanding Restriction Requirement, applicants respectfully request the Examiner to examine the generic linking claims 1 and 23 as required by MPEP 809.

If none of the above-mentioned two requests is not acceptable, applicants suggest that the Examiner issues an election of species requirement in lieu of the outstanding Restriction Requirement so that a proper scope of protection for the invention contemplated by applicants could be sought. For such a case, to expedite the prosecution, applicants provisionally elect amino acid or polypeptide head group which may have optional spacer groups of various classes.

Favorable examination on the merits is requested.

Respectfully submitted,

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